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METHODS

Age-Related Alterations of Doppler Left Ventricular Filling Indexes in Normal Subjects Are Independent of Left Ventricular Mass, Heart Rate, Contractility and Loading Conditions

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The purpose of this study was to determine whether age-related alterations in Doppler diastolic filling indexes occur independent of cardiovascular disease and confounding physiologic variables. Ten old (62 to 73 years) and 10 young (21 to 32 years) healthy male volunteers were rigorously screened for cardiovascular disease and underwent comprehensive Doppler echocardiography, radionuclide ventriculography and invasive measurements of right heart and left atrial pressures. There were no differences between the two groups in the physiologic variables of left ventricular mass, volumes, ejection fraction, end-systolic wall stress, left atrial size, heart rate and right atrial, pulmonary artery, pulmonary capillary wedge and systemic arterial pressures. However, there were marked differences in Doppler left ventricular filling indexes. Compared with the young group, the old group had reduced peak early diastolic flow velocity (56 ± 13 vs. 82 ± 12 cm/s, p = 0.0002) and increased atrial diastolic flow velocity (59 ± 14 vs. 43 ± 10 cm/s, p = 0.009) and had a peak atrial/early flow velocity (A/E) ratio twice that of the young group (1.09 ± 0.29 vs. 0.54 ± 0.15, p < 0.0001). Similar results were obtained for the time-velocity integrals of the peaks. Subjects in the old group also had a markedly reduced peak filling rate (274 ± 62 vs. 348 ± 152 ml/s, p = 0.004). In univariate and multivariate regression analyses, peak early and atrial flow velocities were not related to any of the physiologic variables measured once age was accounted for, although peak filling rate, a volumetric measure of flow, was related to body surface area as well as age.

These results suggest that an altered Doppler diastolic mitral flow profile may be a primary biologic effect of aging, intrinsic to the aged human heart, and may not be explicable by other physiologic and pathologic changes that frequently accompany the aging process.

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Several investigators have demonstrated that the pattern of transmitral diastolic flow measured by pulsed Doppler echocardiography is altered with advancing age, such that early flow is reduced and atrial flow is increased (1–6). Similar findings have been reported with Doppler color flow imaging (2) as well as radionuclide angiography (7), suggesting the possibility of an age-related alteration in left ventricular diastolic function.

However, Doppler diastolic filling indexes have been shown to be altered in early systemic and pulmonary hypertension, as well as in coronary artery, myocardial and valvular heart disease (8–10), all of which are common in the elderly and may be undetected (11–14). Furthermore, recent studies have demonstrated that Doppler and other noninvasive indexes of left ventricular diastolic filling are influenced by heart rate (4,5,9,15–17), preload (9,18–22), afterload (21–23), contractility (15,23) and left ventricular mass (24), all of which have been variably reported to be altered in elderly subjects (9,11,25–35). Therefore, the purpose of this study was to determine whether age-related alterations in Doppler diastolic filling indexes occur independent of cardiovascular disease and confounding physiologic variables. Exclusion of these confounding factors was achieved by a combination of rigorous screening, detailed Doppler echocardiography, radionuclide ventriculography and invasive measurements of right heart and left atrial pressures.

Methods

Study subjects. Subjects were recruited from the Duke University Aging Registry and from Duke University per-

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sonnel under a research protocol approved by the Institutional Review Board of Duke University Medical Center on November 11, 1987. Informed written consent was obtained from all participants. The study groups consisted of 10 young (mean age 25 ± 3, range 21 to 32 years) and 10 old (mean age 67 ± 3, range 62 to 73 years) healthy, community-dwelling male volunteers.

All subjects met the following predetermined screening criteria: 1) a normal history, with no history of hypertension; 2) a normal physical examination, including normal blood pressure determinations obtained on 2 different days by cuff sphygmomometry while the subject was seated (systolic pressure <160 mm Hg in men in the old group and <140 mm Hg in men in the young group and diastolic pressure <90 mm Hg in men in both groups); 3) no participation in competitive athletics, isometric exercise or endurance training; 4) no current or recent medication use; 5) normal values for complete blood count, serum electrolytes and thyroid function test; 6) normal findings on spirometry and arterial blood gas analysis; 7) normal two-dimensional echocardiographic and Doppler color flow examinations; 8) no coronary artery calcification by fluoroscopy; 9) a normal 12-lead rest electrocardiogram (ECG); 10) a normal maximal exercise ECG (all subjects achieved ≥95% of the peak predicted heart rate for age at exhaustion); and 11) normal rest and maximal exercise radionuclide ventriculograms.

Eleven men were sedentary, and nine (five in the young group and four in the old group) participated in regular aerobic exercise, defined as jogging or stationary cycling for at least 20 min, 3 times/week. The young subjects were slightly larger than the old subjects (weight 81 ± 9 vs. 76 ± 3 kg, $p = 0.10$; body surface area 2 ± 0.1 vs. 1.9 ± 0.1 m^2, $p = 0.02$). All subjects were studied under identical conditions, in the postabsorptive state, between 8:00 AM and 11:00 AM.

Doppler echocardiography. Complete two-dimensional, M-mode and Doppler echocardiography was performed immediately before the invasive hemodynamic study by previously described methods (23) using a Hewlett-Packard model 77020CF imaging system fitted with a 2.5 MHz transducer. Pulsed Doppler mitral flow recordings were obtained during quiet respiration at a sweep speed of 100 mm/s, as previously described (23). All recordings were performed by a single sonographer (J.L.P.) who did not know the study hypothesis until after the data were collected. Data analysis was performed off-line with use of a commercially available computer and software system (Nova Microsonics, Inc.) by a single observer (K.H.S.) who did not know from which group the data were obtained. Left ventricular mass, chamber diameter and volume and wall thickness measurements were performed as previously described (23). End-systolic wall stress was calculated by the method of Grossman et al. as previously described, with use of cuff systolic arterial pressure (23).

For each subject, Doppler mitral flow contours from at least three representative beats were traced and analyzed for peak early flow velocity (E), peak atrial flow velocity (A), A/E ratio and time-velocity integrals of each peak as previously described, and the results were averaged (23). The Doppler peak filling rate was derived by multiplying the peak early flow velocity by mitral valve area, a method previously shown in our laboratory (23) to correlate closely with peak filling rate by contrast ventriculography.

Invasive hemodynamic studies and radionuclide ventriculography. After local administration of a 1% Xylocaine (lidocaine) solution, a 7F Swan-Ganz catheter was introduced under fluoroscopic control into the right pulmonary artery by way of the right antecubital vein. At least 30 min after the catheter insertion, with the subject appearing comfortable and the heart rate within 2 beats/min of that during echocardiography, hemodynamic and radionuclide measurements were obtained simultaneously with the subject in the supine position (13,25,36). Mean right atrial and mean, systolic and diastolic pulmonary artery and pulmonary capillary wedge pressures were obtained with Hewlett-Packard pressure transducers and amplifiers and recorded as previously described (13,25,36).

Gated equilibrium radionuclide ventriculograms were acquired for measurement of left ventricular ejection fraction with a Searle LEM mobile gamma camera and a high resolution parallel hole collimator interfaced with an A^2 computer (Medical Data Systems) after injection of 30 mCi of technetium-99m pertechnetate as previously described (36). Radionuclide measurement of ejection fraction was used in this study by prospective design. In our laboratory, radionuclide ejection fraction measurements are highly reproducible and have shown a correlation coefficient of 0.93 (SEM of 0.047) compared with contrast ventriculography (36).

Statistics. Intergroup comparisons were performed with use of the unpaired t test. Univariate and multivariate linear regression analyses were performed using the least squares method to determine the relation of Doppler filling indexes to other measured variables. Significance was established at the level of $p < 0.05$ (by two-tailed analysis). Group data are presented as mean values ± 1 SD.

Results

Hemodynamic measurements (Table 1). Men in the young and old groups had very similar values (p = NS) for hemodynamic variables that could potentially alter Doppler left ventricular filling indexes, although left atrial diameter tended to be larger in the old subjects. Notably, the mean values for left ventricular mass and radionuclide ejection fraction, heart rate and mean right atrial, pulmonary artery, pulmonary capillary wedge and systemic arterial pressures were nearly identical in the two groups.

Doppler left ventricular filling indexes. In contrast, there were dramatic differences between the young and old groups in Doppler left ventricular filling indexes (Table 2, Fig. 1 and 2). The mean value for peak early diastolic flow velocity was markedly lower in the old than in the young group (56 ± 13

Table 1. Potentially Confounding Physiologic Variables in 10 Young and 10 Old Normal Men

Subject No.	Age (yr)	LVM (g)	PWT (cm)	SWT (cm)	EDV (ml)	ESV (ml)	LAD (cm)	HR (min^{-1})	LVEF (%)	MRAP (mm Hg)	SPAP (mm Hg)	DPAP (mm Hg)	MPAP (mm Hg)	PCWP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	ESWS (10^3 dyn/cm^2)
Young																		
1	23	188	1	1.1	126	59	3.1	50	70	8	22	13	18	13	140	73	95	116
2	22	140	0.8	0.8	90	26	2.6	70	64	6	24	12	17	13	128	80	96	76
3	31	167	1.1	0.9	142	47	3.4	80	65	9	20	14	20	8	126	79	95	127
4	28	164	0.8	0.8	123	34	2.6	75	70	6	19	8	12	9	130	78	95	93
5	21	152	0.8	0.9	125	39	2.6	67	67	4	22	10	15	10	138	72	92	93
6	24	163	0.8	1	85	22	2.6	75	63	7	25	6	14	11	116	76	89	147
7	24	178	0.8	0.9	108	30	2.1	56	59	9	27	14	21	16	141	76	98	119
8	25	162	0.8	1	126	44	2.6	48	65	9	26	13	19	12	127	70	95	116
9	27	131	0.8	1	85	38	3.2	55	57	11	33	13	21	14	124	86	99	116
10	28	141	0.1	0.7	88	34	2.8	80	65	5	26	13	18	10	140	70	93	112
Old																		
11	62	140	0.7	0.8	124	49	2.4	60	70	9	23	12	25	14	164	91	115	150
12	66	180	1	1.2	100	70	2.7	68	55	6	26	10	17	9	128	60	83	117
13	69	146	0.9	1.1	68	26	2.8	57	67	8	30	10	19	10	120	62	75	92
14	67	108	0.5	0.8	97	26	3.1	53	57	7	24	9	15	5	110	62	78	90
15	66	138	1	1.1	79	27	3.5	98	74	8	39	12	25	9	126	80	104	142
16	72	155	0.8	0.7	141	67	3.2	84	53	7	34	14	23	11	152	88	109	86
17	76	182	1.2	1.1	84	26	3.2	49	65	10	39	13	25	9	146	70	95	79
18	63	123	1.1	1.3	109	37	3	65	60	5	25	9	15	8	106	60	75	75
19	69	180	1	0.8	186	66	3.2	65	71	4	24	10	16	6	136	80	98	75
20	67	205	1.2	1.2	95	35	3.3	59	67	8	29	12	17	6	144	71	95	97
Mean ± SD																		
Young	25 ± 3	150 ± 27	0.9 ± 0.1	0.9 ± 0.1	110 ± 21	40 ± 12	2.7 ± 0.4	65 ± 12	66 ± 3	7 ± 2.1	26 ± 4	12 ± 3	17 ± 2.7	10 ± 3	130 ± 7	74 ± 6	93 ± 5	105 ± 26
Old	67 ± 3	152 ± 28	0.9 ± 0.2	1.0 ± 0.2	101 ± 21	47 ± 17	3.1 ± 0.3	68 ± 12	64 ± 6	7 ± 1.9	28 ± 6	11 ± 1	17 ± 3.6	9 ± 3	137 ± 18	83 ± 26	96 ± 17	97 ± 52
p	—	0.91	0.35	0.28	0.48	0.35	0.05	0.80	0.50	0.96	0.42	0.36	0.97	0.15	0.45	0.28	0.58	0.31

DBP = diastolic systemic blood pressure; DPAP = diastolic pulmonary artery pressure; EDV = end-diastolic volume; ESV = end-systolic volume; ESWS = end-systolic wall stress; HR = heart rate; LAD = left atrial diameter; LVEF = radionuclide left ventricular ejection fraction; LVM = left ventricular mass; MAP = mean systemic arterial pressure; MPAP = mean pulmonary artery pressure; MRAP = mean right atrial pressure; PCWP = pulmonary capillary wedge pressure; PWT = diastolic posterior wall thickness; SBP = systolic systemic blood pressure; SPAP = systolic pulmonary artery pressure; SWT = diastolic septal wall thickness.

Table 2. Doppler Mitral Flow Indexes in 10 Young and 10 Old Normal Subjects

Subject No.	E (cm/s)	A (cm/s)	A/E	Int E (cm)	Int A (cm)	Int A/E	PFR (ml/s)
Young							
1	87	37	0.42	7.7	3.3	0.42	546
2	60	35	0.58	13.6	2.5	0.18	256
3	97	47	0.48	13.4	5.4	0.41	765
4	72	67	0.92	6	5.4	0.9	394
5	89	55	0.61	14	5.9	0.42	468
6	71	38	0.53	10	3.1	0.31	388
7	99	39	0.39	10	4.8	0.47	565
8	80	33	0.41	12.2	2.7	0.22	475
9	79	44	0.56	11.4	4.6	0.4	365
10	89	41	0.46	11.9	4.2	0.35	263
Old							
11	57	52	0.9	8.3	5.1	0.61	293
12	46	52	1.12	5.4	5.3	0.98	258
13	45	72	1.61	8.9	7.3	0.82	288
14	54	46	0.84	9	6.3	0.7	290
15	72	74	1.02	10.5	6.7	0.64	217
16	46	61	1.34	5.1	4.4	0.86	201
17	63	57	0.9	10	4	0.4	403
18	80	51	0.64	9.6	4.6	0.48	334
19	37	43	1.18	4.2	4.3	1.02	214
20	61	86	1.4	8.2	6.8	0.83	242
Mean ± SD							
Young	82 ± 12	43 ± 10	0.54 ± 0.15	11 ± 2.6	4.1 ± 1.2	0.41 ± 20	448 ± 152
Old	56 ± 13	59 ± 14	1.09 ± 0.29	7.9 ± 2.2	5.5 ± 1.2	0.73 ± 20	274 ± 67
p	0.0002	0.009	0.0000	0.01	0.03	0.002	0.004

A = peak atrial velocity; A/E = ratio of peak atrial to peak early filling velocity; E = peak early filling velocity; Int = integral; PFR = peak filling rate.

vs. 82 ± 12 cm/s, p = 0.0002), whereas peak atrial diastolic flow velocity was increased (59 ± 14 vs. 43 ± 10 cm/s, p = 0.009). The A/E ratio in the old group was twice that of the young group (1.09 ± 0.29 vs. 0.54 ± 0.15, p < 0.0001). Similar results were obtained for the time-velocity integrals of the peaks; the ratio of atrial to early time-velocity integral was 0.73 ± 0.2 cm in the old versus 0.37 ± 23 cm in the young group (p = 0.001). The peak filling rate was markedly

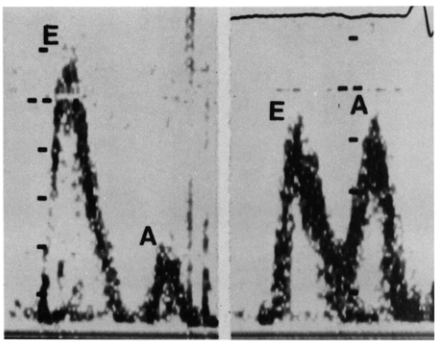

Figure 1. Doppler mitral flow patterns in a representative young **(left panel)** and old **(right panel)** normal subject. A = peak atrial filling velocity; E = peak early filling velocity.

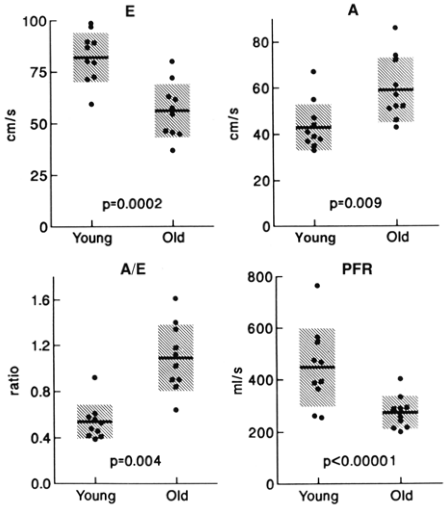

Figure 2. Plots of Doppler diastolic filling indexes in 10 young and 10 old normal subjects. The **solid bars** and **shaded boxes** indicate the mean values ± 1 SD. A/E = ratio of peak atrial to peak early filling velocity; PFR = peak filling rate. Other abbreviations as in Figure 1.

lower in the old than in the young group (274 ± 62 vs. 448 ± 152 ml/s, p = 0.004). Thus, the old group had marked alterations in Doppler filling indexes despite similar results for potentially confounding physiologic variables.

Univariate linear regression analyses (Table 3). These analyses confirmed that the Doppler indexes were independent of the other physiologic variables and strongly associated with age. Values for body surface area appeared to correlate with the Doppler indexes; however, in multivariate analyses, these values did not improve the predictive power of peak early flow velocity, peak atrial flow velocity or A/E ratio after age was accounted for. Values for body surface area were predictive of peak filling rate, a volumetric index of flow, and the relation was independent of age. There were no intragroup or intergroup differences between the men who engaged in regular exercise and those who were sedentary.

The relation of pulmonary capillary wedge pressure to end-diastolic volume was not different between the two groups (0.1 ± 0.04 mm Hg/ml in the young vs. 0.09 ± 0.03 mm Hg/ml in the old group, p = 0.39).

Discussion

Background. Age-related changes in the diastolic transmitral flow pattern by pulsed Doppler echocardiography,

Table 3. Linear Regression Coefficients From Univariate Analysis of Selected Variables Versus Doppler Mitral Flow Indexes

		LVM	LAD	EDV	HR	LVEF	MRAP	MPAP	PCWP	MAP	ESWS	BSA	Age
E	r	0.06	−0.18	0.23	−0.09	0.16	0.16	0.04	0.06	−0.38	0.06	0.59	−0.74
	p	0.86	0.45	0.33	0.7	0.5	0.52	0.95	0.81	0.1	0.81	0.006	0.0001
A/E	r	0.2	0.32	−0.21	0.12	−0.04	−0.08	−0.06	−0.25	0.38	−0.05	0.53	0.81
	p	0.39	0.2	0.44	0.6	0.87	0.72	0.88	0.28	0.1	0.84	0.02	0.0001
PFR	r	0.28	−0.14	0.46	−0.16	0.08	0.06	0.34	−0.09	−0.35	0.15	0.86	−0.59
	p	0.23	0.51	0.04	0.49	0.75	0.8	0.14	0.7	0.13	0.55	0.0001	0.006

BSA = body surface area. Other abbreviations as in Tables 1 and 2.

with reduced early and increased late flow velocities, have been observed previously (1–6). However, other studies have shown that these Doppler left ventricular filling velocities are altered early in the course of a variety of disorders (8–10), most of which are common and sometimes unrecognized in the elderly (3,11–14). Furthermore, recent studies have shown that noninvasive indexes of left ventricular filling are significantly influenced by several physiologic variables, including left ventricular mass and chronotropic, inotropic and loading states (4,5,9,15–23), some of which have been variably reported to be altered by aging (9,11,25–35).

The present study. In the present study, healthy volunteer men were recruited from the community and rigorously screened for cardiovascular, hypertensive, pulmonary and other disease. Two groups of 10 men each, separated in age by 4 decades, underwent comprehensive Doppler echocardiography and invasive hemodynamic studies. Left ventricular ejection fraction was measured by radionuclide ventriculography. The two groups had very similar results for variables that might potentially influence Doppler left ventricular filling mitral flow indexes, including left ventricular mass, volumes and ejection fraction, end-systolic wall stress, left atrial size, heart rate and right atrial, pulmonary artery, pulmonary capillary wedge and systemic arterial pressures. Despite the absence of differences in these potentially confounding physiologic variables, the two groups had markedly different Doppler flow patterns. Subjects in the old group demonstrated reduced peak early flow velocity, increased peak atrial flow velocity and an A/E ratio twice that of subjects in the young group. Subjects in the old group had a reduced peak filling rate as well. In univariate and multivariate analyses, the altered Doppler filling indexes were not related to any of the potentially confounding variables measured once age was accounted for, with one exception. Peak filling rate, a volumetric measure of flow, was independently related to body surface area as well as age.

Significance of present results. The age-related changes in Doppler filling indexes seen in this study were similar in magnitude to those in other reports (1–6). The present results confirm and expand previous data (4,6,37) which suggested that this phenomenon may be independent of gender, body size, left ventricular mass, heart rate, blood pressure and position of the Doppler sample volume. Because peak early flow velocity showed the greatest age-related alteration in the present and previous studies and is relatively sensitive to changes in preload (9,18–22), the similarity of right atrial and pulmonary capillary wedge pressures in the old and young groups in our study is an important finding. One recent study (38) suggested that aging does not alter the Doppler filling pattern of the right ventricle. Although changes in the pliability of the mitral valve (26,39) or in left atrial function (40) cannot be excluded as a cause of the altered diastolic filling, these results suggest that altered diastolic filling may be due to an intrinsic property of the normal aged human left ventricle.

The strong singular influence of age in our study emphasizes that the wide range of age-related normal values for Doppler diastolic flow indexes severely limits the potential utility of Doppler studies for diagnosing diastolic dysfunction in patients and that such studies must carefully control for the effect of age (9,23). For example, in a recent study (41) of left ventricular filling in patients with early hypertension, age correlated more strongly with abnormal Doppler diastolic flow indexes than did any other variable measured, including 24-h ambulatory blood pressure, even though the subjects were relatively young and the group was homogeneous for age.

Whether alterations in Doppler mitral flow patterns, either physiologic or associated with disease, reflect actual changes in myocardial relaxation or compliance is controversial (9,22,42). The present study found no age-related change in the relation of pulmonary artery wedge pressure to end-diastolic volume, and others have also found no age-related effect on rest left ventricular end-diastolic size (32) and pulmonary artery wedge pressure (25,27,29). Although the methods for measuring pressure and volume differed from those of the present and other studies (25,27,29,32), one recent study (28) did report an age-related shift in the relation of left ventricular filling pressure to end-diastolic volume. However, the elderly subjects in that study (28) were patients with chest pain (43) who had received a sedative before the diagnostic study, several had an abnormal ECG and were taking cardioactive medications, and the higher heart rate and systolic blood pressure in this group compared with values in the young subjects may have affected the pressure and volume measurements (43,44). If the altered Doppler left ventricular filling pattern in elderly subjects is due, for example, to age-related changes in myocardial composition (26,45), it would seem likely that would be reflected in measurable differences in myocardial mechanics, but measuring these differences in healthy human subjects (35,42) would not be feasible given the methods currently available.

Potential limitations. Despite the small number of subjects in our study, the observed differences and similarities between the two age groups were potent. Although our subjects were not distributed in a continuum of age, the groups were widely separated in age by an average of 40 years and were similar in all identifiable characteristics. Previous studies (1,2,4,6) have suggested that the age-related changes in Doppler mitral flow indexes are probably continuous and progressive; nevertheless, our results should be confirmed in a study with a larger number of subjects, including middle-aged subjects and women. The invasive methods used for measuring hemodynamic values in the present study provide estimates of preload, afterload and contractility. Although more direct measurements of these variables, as well as detailed invasive measurements of left ventricular relaxation, would be of interest, obtaining direct measurements would involve left heart catheterization and

methods that would not generally be ethically acceptable for use in healthy human subjects.

Although the results may not exclude small residual effects of some confounding variables on changes in Doppler filling indexes with age, they do indicate a high degree of independence from them. The data should not be interpreted to indicate that aging may not induce changes in some variables measured—in particular, left ventricular mass, left atrial diameter and systolic blood pressure—when studied in large groups (11,25–27,32,33). Finally, although the number of old subjects in this study is comparable to the number in the few reports previously available (28–30), a larger group, with women included (46), would be necessary to generate a reliable set of ranges of normal values for right atrial, pulmonary artery and pulmonary wedge pressures in normal, healthy elderly subjects.

Conclusions. The present investigation contributes to our understanding of the phenomenon of an age-related shift in Doppler left ventricular filling indexes by excluding occult disease and a wide variety of physiologic variables as potential confounding mechanisms. Although the mechanisms of this phenomenon remain unclear, our results suggest that an altered Doppler diastolic mitral flow profile may be a primary biologic effect of aging, intrinsic to the aged human heart and not explicable by other physiologic and pathologic changes that frequently accompany the aging process.

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